In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry.*

Special Issue: The Dopamine Hypothesis of Schizophrenia

The dysfunction of the dopamine system is now a well-established component of the neurobiology of schizophrenia. Here, **Howes *et al.*** (pages 9–20) review neuroimaging studies that have examined the dopamine system, including the dopaminergic response to stress, in schizophrenia and its prodrome. Consistent findings identify increased striatal presynaptic synthesis and release of dopamine as the primary source of dopaminergic dysfunction in psychosis. They also review and discuss the underlying genetic risk factors that may moderate the stress response and contribute to the development of psychotic illness. The authors conclude by presenting a model illustrating the interplay between genetics, stress, and dopamine in psychosis.

The dopamine hypothesis of schizophrenia is supported by a large number of imaging studies that identified increases in signaling via the D_2 receptor selectively in the striatum. These findings led to the development of a transgenic mouse model of D_2 receptor upregulation, which has revealed a number of insights into striatal circuit function with direct relevance to the pathophysiology of schizophrenia. **Simpson and Kellendonk** (pages 21–30) review these findings in detail and suggest ways in which this animal model can be used to generate new hypotheses about the disease that can be investigated in human patients.

Molecular imaging studies have provided evidence that forced a reformulation of the dominant model of dopaminergic dysregulation in schizophrenia. These findings indicate that dopaminergic excess in the striatum is most prominent in rostral caudate, while extrastriatal and cortical regions show a deficit in dopamine release capacity. **Weinstein *et al.*** (pages 31–42) describe the regional differential modulation of the dopaminergic signal detected by molecular imaging methods and discuss potential cellular mechanisms that may give rise to this topographically distinct set of findings.

Brain imaging has increasingly revealed heterogeneity in dopamine measures across striatal regions. However, the synaptic underpinnings have only recently been elucidated, enabled through the use of optogenetics in transgenic mice to selectively target dopamine neurons. **Chuhma *et al.*** (pages 43–51) describe how this approach has shown that dopamine neurons signal not only by volume transmission but also in fast synaptic mode, using dopamine, glutamate, and gamma-aminobutyric acid as neurotransmitters to elicit a heterogeneous range of actions across the striatum. Differences in dopamine neuron terminals, presynaptic modulation, and activity contribute further to this heterogeneity, which is likely relevant to the pathophysiology and treatment of schizophrenia.

Schizophrenia has long been thought to involve disturbances in dopamine. Here, **Maia and Frank** (pages 52–66) take a computational perspective to provide an integrated account of a wide range of laboratory and clinical findings in schizophrenia. They argue that two main disturbances, decreased phasic dopamine responses for relevant stimuli and increased spontaneous phasic dopamine release, relate to negative and positive symptoms, respectively, that can each provide a unified explanation for numerous experimental findings in schizophrenia. This concept has implications for the treatment of positive and negative symptoms.

Treating the cognitive deficits of schizophrenia is a major unmet need, as current medications do little to alleviate these symptoms. This review by **Arnsten *et al.*** (pages 67–77) describes strategies for developing compounds to facilitate dopamine's beneficial actions in the prefrontal cortex, a higher brain region necessary for cognition that is a target of pathology in schizophrenia. They focus in particular on dopamine actions at D_1 receptors, which are vital for prefrontal cortical working memory abilities.

Current antipsychotic drugs are not effective for the treatment of cognitive or motivational deficits in individuals with schizophrenia. Selective targeting of biochemical signaling pathways in the brain may lead to novel therapeutic options in schizophrenia. Here, **Urs *et al.*** (pages 78–85) propose a therapeutic approach to target dopamine D_2 receptor biased signaling through β-arrestin–dependent pathways, describe the anticipated effects in different brain regions, and discuss how it may have the potential to treat all symptom domains of schizophrenia.

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